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Review article

Clinical application of transcutaneous oxygen pressure measurements during exercise

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A B S T R A C T

Exertional lower limb pain is a frequent diagnostic issue in elderly patients. Arterial claudication results from the mismatch between the oxygen requirement of, and oxygen delivery to the exercising muscles. Non-invasive vascular investigations (ultrasound imaging, plethysmography or segmental pressure) are used in routine at rest or following exercise, but none can be used during walking or to directly monitor cutaneous oxygen delivery to the limb. Here, we review the methods, tips and traps of the transcutaneous oxygen pressure measurement technique and potential applications.

Transcutaneous oxygen pressure measurement is largely used in vascular medicine for patients with critical limb ischemia. It can also detect regional blood flow impairment at the proximal and distal limb simultaneously and bilaterally during exercise. Exercise-oximetry can also analyze systemic oxygen pressure changes on a reference area on the chest, to screen for occult pulmonary disease. As a surface technique, it does not directly measure muscle oxygen content but provides a reliable estimation of regional blood flow impairment.

With the use of a recently reported index that is independent of the unknown transcutaneous gradient for oxygen, exercise-oximetry provides some accurate information compared to classical non-invasive vascular investigations to argue for a vascular or non-vascular origin of exertional lower limb pain during exercise. Although a time consuming technique, it is a simple test and it is progressively spreading among referral vascular centers as a useful non-invasive diagnostic tool for patients suspected of arterial claudication.

1. Introduction

Peripheral artery disease (PAD) is a major public health challenge. PAD affects approximately 5% of the general population and 20% of people after the age of 70 [1]. The number of PAD patients increased by 23.5% between 2000 and 2010, and patients suffering from PAD have a three-fold increase risk of mortality and major cardiovascular events as compared to non-PAD patients [2].

Claudication is generally the first manifestation of PAD, although PAD may remain asymptomatic for years. Vascular-type claudication is defined as lower back and/or hip and/or buttock and/or thigh and/or calf pain or discomfort that is absent at rest, appears during walking, and forces the patient to stop, thereby impairing walking ability. It can be unilateral or bilateral. Not all patients with PAD report typical vascular-type claudication, and almost half of the patients with PAD have exertional leg symptoms other than intermittent claudication [3]. Apart from PAD, non-vascular disease can induce exertional limb pain that may mimic arterial claudication such as lumbar spinal stenosis [4] or hip osteoarthritis [5]. Further,

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many co-morbid conditions such as cardiac or pulmonary disease can result in walking limitation [6–8] and participate in the walking impairment of PAD patients. The prevalence of comorbidity in patients with claudication is particularly high, specifically in elderly patients. Thereby, defining the exact origin of exertional limb pain can be a challenging issue. Multiple invasive approaches and various non-invasive vascular investigations (NIVI) have been proposed to diagnose the arterial origin of exertional limb pain [4,9]. In this article, we review the methods, tips and traps of the technique and its potential applications.

2. Importance of exercise tests in arterial claudication

In claudication, as in most exercise-related diseases, exercise testing should be used to increase sensitivity and diagnostic performance of any test used. Another benefit of standardized exercise testing is to quantify walking impairment, reproduce symptoms during the medical visit (that may differ from symptoms by history) and screen for associated co-morbid conditions (dyspnea, articular pain) that may also limit exercise. There are various modalities for exercise testing in PAD, but the purpose of this review is not to discuss the strengths or limitations of each approach (constant load *vs.* progressive intensity; treadmill *vs.* corridor walking; walking, tiptoeing) [10–12].

3. Non-invasive exercise tests in arterial investigation

Advantage and limits of various NIVI are reported in Table 1. The most widely used and easiest NIVI is the measurement of resting and post-exercise lower limb arterial pressure generally measured at the ankle and expressed as ankle-brachial index (ABI). ABI, or other segmental pressure examination such as penile, toe or thigh pressure, are recommended by the American College of Cardiology Foundation/American Heart Association to investigate vascular claudication [13]. After a few minutes resting supine period, a sphygmomanometer and a hand-held Doppler are used for the recording of systolic pressures in the brachial, and ankle (i.e., at least posterior tibial, and dorsalis pedis arteries). The ABI is calculated by dividing the highest ankle pressures in each leg by the highest arm pressure [2]. Arrhythmia, intolerance to strict lying position specifically after exercise, arterial stiffness and delay in obtaining readings from the end of exercise, are some of the limits of the technique. Another limit is the heterogeneity of proposed cut-off point to analyze post-exercise ABI results [14]. Last, the diagnostic performance of segmental pressure may be of limited use for proximal claudication [15,16].

Doppler waveform recordings (Table 1, column 2) are used at rest and could be used after exercise. Using a 4–8 MHz continuous Doppler probe, Doppler waveforms can be analyzed at various levels of the arterial tree on both sides before and after exercise. To date, there is lack of consensus regarding normal vs. abnormal waveform interpretation to be found after exercise.

Multilevel resting and post-exercise plethysmography (Table 1, column 3) can be used to quantify blood flow with transient arrested venous return using a thigh cuff abruptly inflated to ~ 50 mmHg. Although the technique is extremely accurate it is mostly used as a research tool rather than use in clinical routine.

Resting and post-exercise thermography (Table 1, column 4) have been abandoned due to environmental constrains and lack of accuracy.

Resting and post-exercise near infra-red spectroscopy (NIRS) has recently been proposed as a rapid and attractive tool to measure muscle oxygen saturation during exercise and diagnose PAD patients specifically at the buttock level [17,18]. Various devices are available that calculate tissue oxygen saturation from the

Table 1
Advantage and limits of various non-invasive vascular investigations.

	Ankle to brachial arterial pressure index indices brachial	Doppler velocity profiles	Plethysmography	Thermography	Near infrared spectroscopy	Scintigraphy	Exercise oximetry
Available in Primary care	Y	Y	Y	N	N	N	N
Simultaneous bilateral measurements	Y	N	Y	Y	Y	Y	Y
Measurement during exercise	N	N	N	Y	Y	N	Y
Differentiation of proximal *vs.* distal ischemia	Y	Y	N	Y	Y	Y	Y
Sensitivity to environmental conditions	N	N	N	Y	Y	N	N
Account for systemic exercise-induced hypoxemia	N	N	N	N	N	N	Y
Normal limits have been validated against radiological imaging	Y	N	N	N	Y	N	Y
Reproducibility	good	good	good	fair	fair	good	good
Cost of the equipment (range in K€) [a]	1–5	2–30	5–20	5–15	30–50	100–300	30–70
Cost per investigation (range in €) [a]	20–100	20–100	20–100	10–50	20–50	300–1000	60–300

[a] Costs of equipment and per investigations are highly variable from one country to another.

absorption of infrared light of multiple wavelengths. There are conflicting results in the literature about the accuracy and reproducibility of the technique [19]. Further contrary to the generally accepted concept that NIRS measures muscle saturation, it has been shown that the majority of the measured signal is derived from a cutaneous source that highly influences the NIRS results [20].

Thallium scintigraphy (Table 1, column 6) has been used to directly estimate muscle perfusion. Although minimally invasive and almost devoid of risk, the irradiation is not negligible and accessibility and cost limit its use to research purpose.

4. $TcPO_2$: an old, well known, NIVI

Transcutaneous oxygen pressure ($TcPO_2$) is an old technique that was based, for years, on Clark–type electrodes reducing oxygen between a silver anode and platinum cathode. Recently a new oxygen analysis technique has become available based on fluorescent response of a photo-chemical probe. Exercise $tcpO_2$ results are quite similar between the two techniques [21]. A one-point calibration to air oxygen partial pressure, according to the barometric pressure, is performed before each experiment. Then, the probe is fixed on the skin by a fixing ring including a doubled sided adhesive. The probe is thus isolated from the ambient air and measures only oxygen diffusing through cutaneous tissues to reach the probe membrane and pass to the reactive area. Local heating to 44 or 45 °C allows for maximal local vasodilation, but $TcPO_2$ remains lower than underlying tissue despite automatic temperature-correction of PO_2 to 37 °C. Local heating makes the technique relatively insensitive to environmental conditions. Many factors can influence the gradient between the cutaneous and deep tissue level including sub-cutaneous fat, edema, local consumption, capillary density. This gradient is not predictable. It can vary with probe positioning but is constant over time once the probe is heated and fixed to the skin. This gradient is a limitation of the technique. Since the skin is the final tissue for oxygen delivery and most subject to oxygen debt in severe PAD, $TcPO_2$ has appropriately been used in the quantification of severe ischemia. It has been used since the early 1960s at rest in severe PAD and in the 1980s with exercise for patients with claudication [22–28]. In this latter case, although some authors used only limb probes, most publications used a chest reference probe to account for systemic changes in arterial PO_2 assuming that chest-$TcPO_2$ changes during exercise satisfactorily reflect arterial PO_2 changes [29]. While recent publications still recommend use of $TcPO_2$ for the evaluation of critical limb ischemia, in early stages of PAD, specifically claudication, Exercise-$TcPO_2$ was abandoned in the 1990s. The principal reason for giving up Exercise-$TcPO_2$ was the lack of reliability of the technique expressed as absolute limb changes or as limb changes divided by chest changes (regional perfusion index) [24,30–33].

5. Reasons for a renewed interest in Exercise-$TcPO_2$

Beyond the analysis of limb $TcPO_2$, the analysis of chest $TcPO_2$ changes is a new and original approach in PAD patients. Due to the sigmoid relationship of the saturation to PO_2 relationship in arterial blood, saturometry is relatively insensitive to falls in arterial PO_2 if arterial PO_2 is high at baseline. Changes in $TcPO_2$ may show an unexpected chest $TcPO_2$ decrease during exercise [29,34] that seems predictive of underlying pulmonary dysfunction. As suggested in the literature, the oxygen debt during walking can be a cause of exercise pain [35] that is likely to worsen pain in case of already impaired limb perfusion. Example of chest $TcPO_2$ changes are presented in Fig. 1.

At the limb level, the decrease from resting oxygen pressure (DROP) calculation allows one ignore the transcutaneous gradient

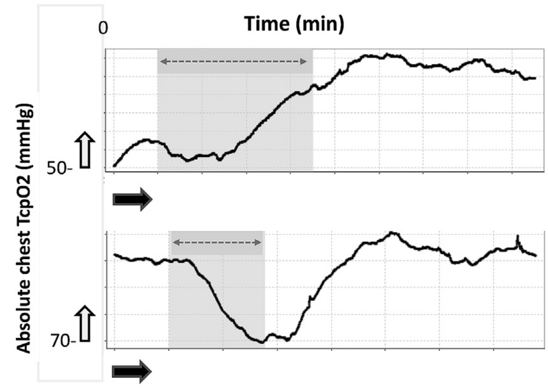

Fig. 1. Typical examples of exercise chest transcutaneous oxygen pressure ($TcpO_2$) changes.
Normal (A) and abnormal (B) chest $TcpO_2$ changes. The grey rectangle is the walking period. The lower panel was observed in a 60-year female with severe pulmonary interstitial disease. Note that the absolute starting pO_2 is high because the patient is under permanent oxygen treatment (2 l/min). White large arrows are 10 mmHg and black large arrows are 2 min. Grey arrow in dash line is the walking period.

issue. The DROP index is the absolute change in $TcPO_2$ from resting value of each of the limb probes, corrected for the absolute change in $TcPO_2$ from resting value of the chest probe. The formula of the DROP is as follows: DROP = $[PO_{2(site)}t_t - PO_{2(site)}t_0] - [PO_{2(chest)}t_t - PO_{2(chest)}t_0]$.

Where $PO_{2(site)}t_t$ is the oxygen pressure at a limb site at time; $tcPO_{2(site)}t_0$ is the oxygen pressure at a limb site at time 0, which corresponds to mean oxygen pressure at the site measurement probe within the baseline time; $PO_{2(chest)}t_t$ is the oxygen pressure at a chest site at time t; and $PO_{2(chest)}t_0$ is the oxygen pressure at a chest site at time 0, which corresponds to mean oxygen pressure at the chest site within the baseline time.

The DROP index is expressed in mmHg. By construction, the DROP at baseline (t0) is zero, and an increase in the chest to limb difference is a negative value. From the whole recording the minimum DROP value (DROPmin) during or following exercise can be retrieved. The DROP being independent from absolute starting value the thickness of subcutaneous fat at the buttock level does not impair its accuracy in the evaluation of buttock exercise-induced ischemia. While distal PAD is typically characterized by calf pain as in the Rose/WHO questionnaire [36], proximal PAD is characterized by buttock or hip pain and relies on either aortic, common iliac and/or isolated internal iliac lesions [9,37,38], which is better characterized in the Edinburgh questionnaire [39]. The prevalence of proximal claudication ranges 5–15% among PAD patients with claudication [38,40] but appears much higher among patients with patent aorto-bi-femoral bypasses [41] or after bilateral internal iliac artery (IIA) embolization [42]. Usual arterial tests may remain within normal limits and penile pressure and NIRS showed low sensitivity to detect arterial compromised perfusion at the proximal locations [19].

Overall, although $TcPO_2$ recording is a surface value, it allows for the specific analysis of oxygen delivery/consumption on regional areas of interest simultaneously not only during or following exercise but throughout exercise and recovery bilaterally from the lower back to foot level [43]. Typical examples of multilevel limb recording are presented in Fig. 2.

6. Additional value of Exercise-$tcPO_2$

As compared to usual non-invasive techniques (ABI, ultrasound, penile pressure), exercise-$tcPO_2$ appears of particular interest at the

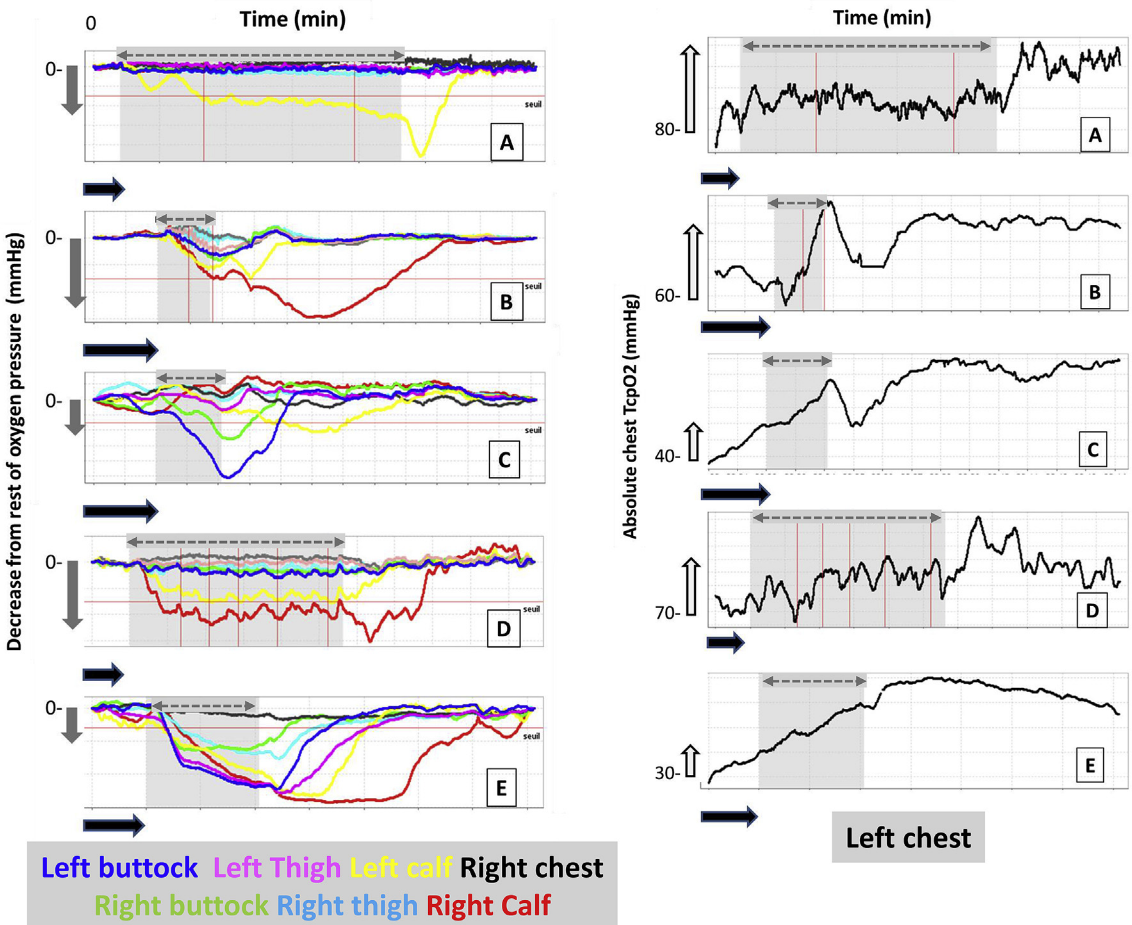

Fig. 2. Typical exercise-transcutaneous oxygen pressure recordings.
(Left panel) Typical examples of multilevel limb recording. Grey arrows are −25 mmHg and black arrows are 2 min. Vertical red lines are event markers. Horizontal red lines are the limit for normal responses. The grey rectangle is the walking period. From top to bottom: (A) isolated non-limiting left calf ischemia, (B) isolated limiting right calf ischemia, (C) bilateral limiting buttock (left more than right) ischemia and moderate left calf ischemia, (D) bilateral limiting (right more than left) calf ischemia, (E) all six locations (buttocks; thighs and calves) ischemia with severe and prolonged ischemia on the right calf after exercise. (Right panel) Absolute corresponding chest changes observed. White large arrows are 10 mmHg and black large arrows are 2 min. Grey arrow in dash line is the walking period.

buttock level for proximal claudication [9,37,38] where these non-invasive techniques lack sensitivity [15,16,44] resulting in prolonged diagnostic error [40]. Chest $tcpO_2$ changes also allow for the detection of exercise-induced hypoxia [29,34] leading to the diagnosis of occult pulmonary diseases [6]. Further, Exercise-$tcPO_2$ allow for the diagnosis of segmental ischemia such as isolated foot and thigh ischemia [43]. It is of interest to note that, even in patients with an abnormal resting ABI (<0.90), Exercise-$tcPO_2$ can remain within normal limits in almost 20% of patients, suggesting various non-vascular etiologies as principal causes of walking impairment [45]. Last, based on a multicenter analysis of practice, the use of the technique in those with atypical claudication or claudication of doubtful vascular origin result in significant modifications of the initial diagnostic hypotheses and improved test selection resulting in cost reduction [46].

7. Standard validated method to perform Exercise-$tcPO_2$

The methodology for the tests has been previously described including a video about technical tricks and traps [37]. In brief, a reference probe is placed on the chest to measure systemic changes. Depending on the number of available electrodes and reported localization of pain, probes are positioned on lower back, buttocks, thighs, calves, or feet. Before fixing the electrode, the skin is cleaned and dead cells from the epidermal surface are removed by gently rubbing the skin with gauze. Once the probes are in position, a pretest heating period of 15 min in the standing position is required to allow optimal local skin temperature to be reached.

Supplementary video related to this article, showing the method and typical results, can be found at https://doi.org/10.1016/j.atherosclerosis.2018.07.023.

The treadmill test is performed using a constant 10% slope and 2 MPH (3.2 km/h) speed reached within a minute. Patients are encouraged to perform at the highest possible speed for the longest time possible. Exercise is discontinued on the patient's request at the point of maximal pain tolerance (and not at pain occurrence).

$TcPO_2$ values are recorded for 2 min in the standing position before the treadmill test starts, during the walking period, and for at least 10 min in the standing position after the end of walking. The data are recorded on a computer on a 0.5 Hz basis through a custom-made program. The decrease from rest of oxygen pressure (DROP) index is calculated in real-time by a dedicated software [37].

8. Validation and application studies of Exercise-tcPO_2

DROPmin at exercise is highly accurate and reliable in predicting the presence/absence and severity of angiographically proved lesions at both the buttock and ankle levels. Consistent with previous results at the buttock [37] and distal level [47], the presence of ischemia on limb TcPO_2 probes during exercise are defined as a minimal DROP value below −15 mmHg. This method was shown to provide a 79% sensitivity and 86% specificity for detection of lesions in arteries toward the hypogastric circulation on arteriograms when the cutoff point is minus 15 mmHg [37], and was shown to be more accurate and reliable than near infra-red spectroscopy (NIRS) [19], or penile pressure measurements [16]. It has also proved high reliability [48]. Additional validation of the technique against computed tomography angiography has recently been reported resulting in nearly identical objectively defined cut-off point and a comparable diagnostic performance [49,50].

8.1. Tips, tricks and traps in exercise oximetry recordings

A few technical or clinical points of interest are to be underlined as follows:

- The use of multi-probe devices increases the risk of disconnections. Nevertheless, the use of large overlying adhesives and circumferential nets reduce this risk to less than 2 per thousand of expected measurements [51].
- Any TcPO_2 value above 100 mmHg is suspect of the presence of an air bubble in the fixation ring.
- Users should avoid shaving hair from the skin where probes are to be placed, which may increase the O_2 delivery to the probe.
- Probes should not be placed in skin concavities that may negatively impact on the contact between the probe and the skin.
- Standing in position for 10–15 min both before and after the walking period is better tolerated if the patient can hold hand rail.
- The choice of probe position is controversial. Standard positions are generally used (e.g. buttocks and calves) or probes are positioned at the region of pain from patient's history. The optimal choice seems to be a mix of standard positioning and saving one probe for a specific location if any.
- One must be cautious in interpretation of results when the symptoms on treadmill do not reproduce the symptoms noted by patient history or are not consistent with probe position.
- To date, very little is known on the effect of different treadmill protocols (incremental vs. constant load) or the duration of walking in constant load tests on the results of Exercise-TcPO_2. The choice can also be made to use a combined constant load phase followed by an incremental phase. This allows each patient to reach symptom limitation while decreasing the risk of reaching the cardiorespiratory limit before the claudication as often occurs in incremental exercise tests.
- There is a risk of drift in TcPO_2 values than can either result from electronic drift or more often from an insufficient initial warming period. Prolonged pre-test heating of the skin is required to reduce this risk. The drift can be easily estimated and corrected if the recovery period is long enough to allow a return to sTable resting values.
- DROP should be approximately zero at end recovery and if not suggests insufficient recovery duration or presence of a drift.
- DROP is independent for starting absolute values but, attention should nevertheless be paid to the absolute starting value. Indeed, in case of severe chronic ischemia a very low starting value (e.g.: 10 mmHg) cannot mathematically result in a major decrease (DROP) during exercise.
- A change in the DROP index may be seen only after the walking period, with no significant change seen while walking. In this situation, specific attention must be paid for a possible decrease in the chest reference value during exercise, in case of exercise-induced systemic hypoxemia.

9. Gaps in knowledge about exercise-TcPO_2

To date, there is evidence of the correlation between DROP minimal value and the presence of radiological stenosis or occlusions of arteries, but evidence is still missing of the concordance between TcPO_2 (a surface skin value) and muscle abnormal perfusion as could be estimated from muscle scintigraphy.

A simplification of the constant load followed by incremental load protocol may be helpful for the routine use of the technique. The pre-test heating period should not be reduced, but limiting the walking period could save time. To date, it is not proven that a test limited to 5 min of walking is sufficient to provide accurate information vs. a protocol with prolonged walking.

At present the exact place of Exercise-TcPO_2 among NIVI in the diagnostic algorithm of exertional limb pain is undefined. Intuitively, the test would be best proposed for use in patients suffering atypical claudication [52] or claudication of doubtful vascular origin or if usual non-invasive investigations are incomplete or not sufficient. In fact, due to the high number of co-morbid conditions observed, presently Exercise-TcPO_2 is proposed in Angers to all patients with vascular-type claudication. Whether or not contrast-enhanced imaging has to be done in patients with claudication but a normal Exercise-TcPO_2 result remains to be defined. Computed tomographic angiography or magnetic resonance angiography, are expensive tools and have the risk of renal or allergic complications. Use of exercise-TcPO_2 may help better select patients for these tests and therefore reduce both cost and risks of contrast-enhanced imaging. Cost (and reimbursement) of Exercise-TcPO2 remains an issue. In France and other countries, absence of reimbursement remains a limitation to the development of the technique although, recent evidence from the CINEY study suggests that use of exercise oximetry could significantly modify diagnostic hypotheses and result in the reduction of the cost for diagnostic tests [46].

Beyond diagnosis, Exercise- TcPO_2 is of interest to follow the beneficial effect of treatments [53,54] but to date has not proved ability to predict treatment results. Of specific interest in this area is chest profile classification. The chest classification is robust but whether or not the presence of an abnormal chest response should contra-indicate revascularization or is predictive of a mediocre functional result of revascularization (in term of improvement in walking capacity) remains to be defined.

Last, potential applications in the non-vascular area are still to be evaluated. PAD and lumbar spinal stenosis (LSS) are both frequent diseases and then a major health and economic problems. Nearly 10 million Americans experience PAD whereas an estimated 2.4 million Americans will be affected by LSS by the year 2021 [55]. The resulting improvement in function after LSS surgery, are far from optimal. Could it be that non-satisfactory results are in part due to undetected PAD and proximal ischemia? Whether or not the presence of the proximal ischemia in lumbar spinal stenosis patients predicts the poor outcomes after spinal surgery and would justify a pre-operative screening of patients with lumbar exercise-induced pain, is a fascinating question for future research.

10. Conclusion

Exertional lower limb pain is a diagnostic issue in elderly

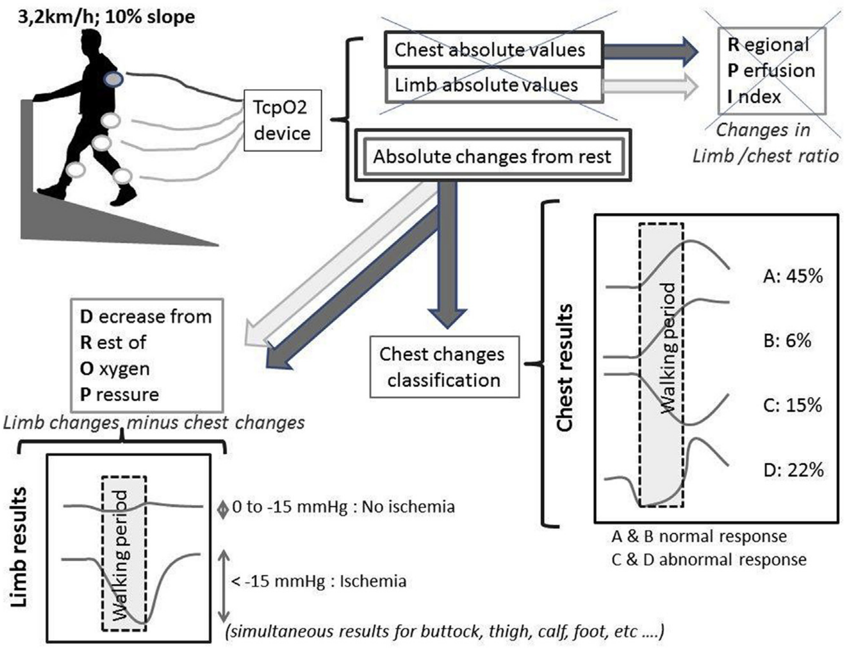

Fig. 3. Overview of the concept and clinical interest of exercise oximetry.
Classification of chest changes is issued from Refs. [29,34]. The cut-off for the presence of limb ischemia is issued from Refs. [37,47,48,50].

patients with frequent co-morbid conditions that may impair walking ability. Transcutaneous oxygen pressure ($TcPO_2$) is a non-invasive technique than can detect regional ischemia at different level and on both sides simultaneously, and can also detect exercise-induced hypoxemia. Exercise-$TcPO_2$ is developing in referral centers in France and abroad as an attractive additional tool in the diagnosis of atypical claudication or of exercise-induced limb pain of questionable vascular origin. Exercise-$TcPO_2$ adds clinical information compared to usual NIVI. It is highly accurate to detect lesions on the arterial tree toward the pelvic circulation (i.e. aorta, common iliac and internal iliac). It can detect walking-induced transient hypoxemia using the chest probe in patients with claudication. The overview figure (Fig. 3) summarizes these different points.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

PA wrote the first draft. NO, SH, PA participated to data analysis SH reviewed and corrected the draft. All authors have critically reviewed the manuscript on the scientific content and have approved the final version of the manuscript.

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